REMARKS

Claims 1-11 and 13-74 are pending in the present application. Claims 1-11, 13, 27-42 and 63-74 were examined in the Office Action dated October 18, 2007. Claims 14-26 and 43-62 have been withdrawn from consideration after a restriction requirement.

Applicants appreciate the Examiner's decision to rejoin and examine Group III claims 27-42 and 63-64. An updated listing of the claims is provided, to reflect that the status of claims 27-42 has changed from "withdrawn" to "previously presented". Additionally, the status of claims 1 and 13 has changed from "currently amended' to "previously presented", and the status of claims 65-74 has changed from "new" to "previously presented".

Claim Rejections - 35 USC § 103

Claims 1-11, 13, 27-42 and 63-74 were rejected under 35 U.S.C. 103(a) as being unpatentable over Mills (WO 00/29037) in view of Cook (US 6206931). The Office Action stated that Mills `037 fails to teach that the sterilizing process for treating an implant also comprises applying tension to the soft tissue at least during part of step (b) or during each of steps (a)-(c). However, the Office Action relied on Cook `931 for its disclosure that an implant tissue can be conditioned by the prolonged application of a load on the longitudinal axis or preconditioned by stretching in the lateral dimension.

The Office Action acknowledged that Cook `931 "appears to disclose that the tensioning step occurs **after** the disinfection steps..." (page 4 (emphasis added)). Nonetheless, the Office Action concluded that it would have been obvious to provide the tensioning step during one or all the steps of the disinfection process of a soft tissue in order to obtain a properly conditioned/tensioned connective tissue graft to implant in a patient.

In their previous response, Applicants pointed out that there are reasons why one would not do so based on the teachings of Cook `931. For example, it would be more cumbersome to apply tension or stretching **during** a disinfection process (when the implant is immersed, submersed or showered in a liquid medium containing the

disinfecting agent – see Cook `931, col. 6, lines 61-67) than **separate from** a disinfection process (as Cook `931 teaches).

The final Office Action dated October 18, 2007 stated that Applicants' arguments were not persuasive. The Office Action stated that it would have been obvious to **combine both steps into one step** in order to optimize the processing method by shortening/decreasing the processing time through processing the implant in a parallel fashion rather than in a serial fashion. (Page 10 (emphasis added)). The Office Action also stated that "It would have been obvious to one of ordinary skill in the art at the time of invention that there is a reasonable expectation of success, with only the expected results attained." (Id.).

Under the USPTO's current guidelines on obviousness, a claim may be rejected for obviousness based on a rationale of "combining prior art elements according to known methods to yield predictable results." See Manual of Patent Examining Procedure, §2143, p. 2100-129 (Rev. 6, 8th Ed. (Sept. 2007)). However that rationale requires, *inter alia*, findings by Office personnel that:

2) a finding that one of ordinary skill in the art could have combined the elements as claimed by known methods, and that in combination, each element merely performs the same function as it does separately;

(3) a finding that one of ordinary skill in the art would have recognized that the results of the combination were predictable;

Neither of these findings can be made here, which indicates that the rejection should be withdrawn.

There is no finding that the conditioning techniques used in Cook `931 could be adapted to the process of Mills `037 using **known methods**. Cook `931 discloses that a segment of tela submucosa segment can be preconditioned by longitudinal or lateral stretching, for example by suspending a weight from the segment. (Cook `931, col. 11, line 62 to col. 12, line 3). The Office Action does not include any finding that there is a

known method of applying Cook's conditioning techniques **during** the sterilization process disclosed in Mills `037.

Furthermore, there can be no finding that each element in combination merely performs the same function as it does separately, or that the results of the combination were predictable. To the contrary, Applicants have shown that the claimed process yields **unexpected results**. Applicants have shown that applying tension to tendons during the sterilization process yield tendons having improved strength as compared to non-tensioned tendons.

The present specification explains: "Moreover, it has surprisingly been found that less damage arises from contact with a peroxide when tension is applied to a soft tissue than when no tension is applied, as in conventional methods." (Specification, paragraph 53). Table 1 in Applicants' specification shows the effects on tendon samples from exposure to various chemicals, including hydrogen peroxide (an oxidizing sterilant) and detergent. The effect of the various chemicals as measured by collagen degradation in the tendon is shown in Table 1, with a higher number indicating more denatured collagen and thus more damage to the tendon. The results in Table 1 show that exposure of the tendon samples to peroxide resulted in denatured collagen in the tendon samples, but when tension was applied to a tendon during the tendon's exposure to the peroxide, there was less collagen degradation.

The Office Action indicated that the collagen degradation results set forth in Table 1 were not persuasive as to whether there is an unexpected benefit of tensioning while a peroxide is applied. First, the Office Action stated that the difference in the level of denatured collagen was "not statistically significant". Applicants submit that the Office Action does not provide any statistical analysis to support this conclusion. Moreover, the collagen degradation measured for the non-tensioned implants was higher than for the tensioned implant; even considering the standard deviation, the results do not overlap. Applicants submit that the Office Action improperly disregarded the results set forth in Table 1 of the specification. Second, the Office Action stated that the load test results in Table 1 were obtained when both peroxide and detergent were

used on the implant. Applicants submit that this point is irrelevant and not a basis to disregard the test results, since the present claims do not exclude using a detergent with a peroxide or other oxidizing sterilant. For example, step (b) in claim 1 recites "contacting the implant with an oxidizing sterilant." This would include the step of contacting the implant with peroxide and detergent.

To further show that the claimed process yields unexpected results, Applicants are submitting the Declaration of Arunas A. Zhukauskas ("the Zhukauskas Declaration").

The Zhukauskas Declaration describes a recent study that evaluated the effect of applying tension to soft tissue implants during a sterilization process. (Zhukauskas Declaration, ¶ 5). In order to confirm that tensioning during the sterilization process would have an effect on tendon strength after the sterilization process, an assortment of tendons were tested from various donors. (Id.) For each pair of tendons obtained from a single donor, one tendon of the pair was subjected to a sterilization process while tension was applied. (Id.) Tension was applied to the tendons by placing the tendons on tensioners similar to those shown in Figure 4 of the present application. (Id.) The tensioned tendons were then placed in the chamber used for the sterilization process, and they remain tensioned throughout the sterilization process. (Id.) The contralateral tendon (the other tendon of the pair from the opposite leg of the same donor) also underwent the same sterilization process at the same time, except that no tensioning was applied to the contralateral tendon during the sterilization process. (Id.) Therefore, the study design allowed a paired comparison between tendons from the same donor to be performed. (Id.)

The tensioned and non-tensioned tendons were subjected to the same sterilization process. (Zhukauskas Declaration, ¶ 6). The sterilization process included the steps of contacting the implant with a protective agent selected from the group consisting of alcohols and polyols; contacting the implant with an oxidizing sterilant; and contacting the implant with a rinsing fluid. (Id.) The sterilization process included other steps as well. (Id.)

After the sterilization process, all tendons from the study were tested on a material testing machine in a tensile manner until failure in order to determine the strength of each sample. (Zhukauskas Declaration, ¶ 7). Each tendon was subjected to the same test protocol, which included the application of a pre-defined and automated load profile, culminating in a pull to ultimate failure load for that tendon. (Zhukauskas Declaration, ¶ 8).

Tables 3 and 4 from the Zhukauskas Declaration list the relative pull strengths that were measured for each tendon in this study. (Zhukauskas Declaration, ¶ 9). Ultimate Tensile Force is the absolute amount of force causing the tendon to fail, or rupture. Ultimate Tensile Stress is the same measurement normalized for the cross-sectional area of the gage length of the tendon.

Table 3: Ultimate Tensile Force (UTF) per sterilized tendon

Tendon Type	Donor #	*T (N)	*NT (N)
Posterior Tibialis	52720	2618	878
Achilles	53403	5889	3119
Peroneous Longus	48726	3298	1636
Anterior Tibialis	48359	2645	1810
Anterior Tibialis	50341	3537	2862
Posterior Tibialis	50341	2881	2499
Peroneous Longus	49928	3370	1370

* T=Tensioned, NT=Not/non-Tensioned, N=Newtons

Table 4: Ultimate Tensile Stress (UTS) per sterilized Tendon

Tendon Type	Donor #	*T (MPa)	*NT (MPa)
Posterior Tibialis	52720	119.6	21.12
Achilles	53403	83.98	56.94
Peroneous Longus	48726	109.3	48.85

Anterior Tibialis	48359	141.0	90.12
Anterior Tibialis	50341	166.9	137.3
Posterior Tibialis	50341	192.9	165.4
Peroneous Longus	49928	119.6	21.11

* T=Tensioned, NT=Not/non-Tensioned, MPa=megapascals

These results show a clinically relevant difference between tensioned, sterilized tendons and the non-tensioned, sterilized tendons, with respect to the properties of ultimate tensile force and ultimate tensile strength. (Zhukauskas Declaration, ¶ 10). This indicates that applying tension to the tendons during the sterilization process yields tendons having improved strength as compared to non-tensioned tendons, in that more tensile force was required to cause the tendons to fail. (Id.) The non-tensioned tendons failed more easily (with less force applied) than the tensioned tendons. (Id.)

A statistical analysis was performed on the data in Tables 3 and 4. (Zhukauskas Declaration, ¶ 11). The statistical analysis showed that there is a statistically significant difference between the tensioned, sterilized tendons and the non-tensioned, sterilized tendons, with respect to ultimate tensile force and ultimate tensile strength. (Zhukauskas Declaration, ¶ 12). On average, the tendons that were not tensioned during the sterilization process were 1438 N weaker (p-value= 0.004) than the tendons that were tensioned. These tendons also showed a decrease of 56.05 MPa, on average (p-value=0.003), compared to tensioned tendons.

Applicants submit that the final Office Action failed to establish a prima facie case of obviousness with respect to 1-11, 13, 27-42 and 63-74. The Office Action does not make the factual findings required for a rationale of obviousness. Applicants have shown that the claimed process yields unexpected results. Applicants have shown that applying tension to tendons during the sterilization process unexpectedly yields tendons having improved strength as compared to non-tensioned tendons. Accordingly the rejection of claims 1-11, 13, 27-42 and 63-74 should be withdrawn.

The final Office Action also rejected claims 6 and 69 under 35 U.S.C. 103(a) as being unpatentable over Mills (WO 00/29037). The Office Action acknowledged that Mills `037 does not specifically teach that the implant contains an amount of alcohol in the implant before carrying out the step of contacting the implant with an oxidizing sterilant, as recited in claims 6 and 69.

Applicants submit that this rejection is based purely on speculation as to whether alcohol remains in the implant after step 2 in Table I in Mills `037. The Office Action is incorrect that the only fluid removal step mentioned by Mills `037 is after step 4 in Table I; Mills '037 teaches that the cleaning fluid can be removed after any of steps 1, 2, 3 and/or 4 in Table I. The Office Action is also incorrect that oscillating the pressure in the chamber in step 4 is the only means of removing the cleaning solution. Accordingly the rejection of claims 6 and 69 should be withdrawn.

The Office Action rejected claim 28-30 under 35 U.S.C. §103(a) for obviousness based on Mills `037 in view of Cook `931, and further in view of Grood and Noyes (Journal of Bone and Joint Surgery, 58:1083-1088 (1976)). The Office Action relied on Grood and Noyes as disclosing that an implant is subjected to tension in the ranges of 0.5 Newton to about 20 Newtons, or from about 1 to about 10 Newtons, or from about 3 Newtons to about 5 Newtons in order to ensure that the implant has necessary mechanical properties to function properly when implanted.

Applicants submit that Grood and Noyes is not relevant or analogous art to processes for making an implant comprising soft tissue more suitable for implantation into a recipient. Grood and Noyes evaluated the mechanical properties of the Richards polyethylene ligament implant and found that the ligament deformed at a force of 420 newtons. Grood and Noyes relate to evaluating the strength of synthetic ligament implants compared to human anterior cruciate ligaments, not to sterilizing implants or making an implant more suitable for implantation into a recipient. There is absolute nothing in Grood and Noyes that suggests an implant comprising soft tissue should be subjected to tension during contact with one or more cleaning agents.

Furthermore, Grood and Noyes do not teach or suggest the particular ranges set forth in claims 28-30. The Office Action relies on Figs. 2 and 5 as disclosing the claimed ranges, but those figures have y-axes extending from 0 to 600 newtons and 0 to 2000 newtons, respectively. Neither of those figures discloses the much narrower ranges of claims 28-30, namely from 0.5 Newton to about 20 Newtons, or from about 1 to about 10 Newtons, or from about 3 Newtons to about 5 Newtons.

Accordingly the rejection of claims 28-30 should be withdrawn.

Petition for a Three Month Extension of Time

Applicants hereby petition for a three-month extension of time in which to respond to the Office Action of October 18, 2007. The Commissioner is authorized to charge the requisite extension fee of $1050.00, and any necessary fees for this submission, to the Deposit Account of McAndrews, Held & Malloy, Account No. 13-0017.

CONCLUSION

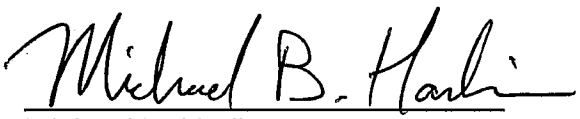
For the foregoing reasons, Applicants submit that claims 1-11, 13, 27-42 and 63-74 are in condition for allowance.

The Examiner is invited to telephone Applicants' representative to discuss any questions or if Applicants' representative may be of any assistance to the Examiner in the reconsideration and allowance of this case.

The Commissioner is authorized to charge any necessary fees to the Deposit Account of McAndrews, Held & Malloy, Account No. 13-0017.

Respectfully submitted,

Dated: April 18, 2008



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